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administering to the vertebrate a DNA transcription unit comprising DNA encoding an antigen of the influenza virus operatively linked to DNA which is a promoter region, in a physiologically acceptable carrier, wherein the DNA transcription unit is expressed in cells of the vertebrate, [thereby eliciting a humoral immune response, a cell-mediated immune response, or both, against the antigen,] whereby the vertebrate is protected from disease caused by the influenza virus.

Remarks

Claims 1, 16, 17, 32, 44 and 52 have been amended to delete the phrase "thereby eliciting a humoral immune response, a cell-mediated immune response, or both, against the antigen". The type of immune response that is generated by the DNA transcription unit is immaterial; the critical factor is protection against disease.

Claims 1-3, 5-7, 9-26, 28-38 and 40-56 are pending.

Applicants note that the Examiner has not addressed or reiterated certain rejections from the previous Office Action (Paper Number 11, mailed from the U.S. Patent and Trademark Office on August 7, 1995). In particular, the Examiner did not state whether the following rejections were maintained or withdrawn:

the rejection of Claims 45-49 and 53-56 under section 112, first paragraph, as set forth in paragraph 4 of the previous Office Action; and

the rejection of Claims 1, 16, 17, 32, 44, 52 and 53 under section 112, second paragraph, as set forth in paragraphs 5 and 7.

Applicants respectfully request that the Examiner indicate whether these rejections have been withdrawn, or are maintained.

Objection to the Specification under 35 U.S.C. 112, first paragraph

The Examiner objected to the Specification, stating that "Applicants have not enabled a method of immunizing vertebrates against any infectious agent." In particular, the Examiner expressed concern about the model for HIV infection. While the Examiner acknowledged the teachings of *Almond et al.* (Lancet 345:1321-1344 (1995)) that infection of macaques with simian immunodeficiency virus (SIV) is a model for HIV infection in man, it is Examiner's opinion that "This doesn't mean that rhesus macaques are a good model for HIV infection."

Applicants respectfully request clarification of the Examiner's statement that the model is not a "good" model. The use of nonhuman primates is an accepted, and highly regarded, model for the study of AIDS and HIV infection. Because of similarities between structure and pathologic consequences of simian immunodeficiency viruses and human immunodeficiency viruses, primates are extremely important models for AIDS research:

HIV-1 and HIV-2 are members of a large family of closely related primate lentiviruses. The other family members are known as simian immunodeficiency viruses (SIVs). Whereas most of these simian viruses have proven to be non-pathogenic in their natural host species, some have been shown under experimental conditions to induce an AIDS-like disease in certain Asian monkeys (citations omitted). *The structural homologies of these simian viruses with HIV and the similarities in the pathologic consequences of their infection in non-human primates to AIDS make these extraordinarily powerful models for the study of AIDS. Thus, HIV- and SIV-infected non-human primates remain the most important systems for studying AIDS.*

(Emphasis added; see Letvin, N., *Current Opinion in Immunology* 4:481-485 (1992), a copy of which is attached as Exhibit A)). It is unclear to Applicants how such a highly regarded and frequently used model is nevertheless not a

"good" model for infection. The Examiner is respectfully requested to provide support for his assessment.

The Examiner also expressed concern regarding the data submitted in the Declaration under 37 C.F.R. 1.132 of Dr. Harriet L. Robinson. It is acknowledged that the DNA immunizations did not prevent infection or protect against CD4+ cell loss. However, Applicants are not claiming protection against infection, but rather, protection against disease. Protection against disease differs from protection against infection: an immunized vertebrate may be infected, yet may not exhibit the pathology of disease. As stated in the Specification at page 7, lines 5-8, immunizing indicates that the immunized vertebrate is protected, partially or totally, from the manifestations of infection (i.e., disease) caused by the infectious agent. The data described in the Declaration meets this standard for protection. During the time period of the study, the vaccinated animals did not demonstrate any clinical signs of disease (AIDS). Thus, these animals were "protected against disease", as stated in the claims, during the course of the study.

Applicants have demonstrated protection against disease for a range of diseases, including influenza, immunodeficiency virus, and rotavirus. Applicants have also demonstrated protection against measles, as described in the Second Declaration under 37 C.F.R. 1.132 of Dr. Harriet L. Robinson. An unexecuted copy of the Second Declaration is being filed concurrently with this Amendment. The executed Second Declaration will be filed as soon as it is available. The Second Declaration provides data indicating that mice vaccinated with DNA transcription units containing measles antigens, particularly hemagglutinin and/or fusion protein antigens, raised an immune response that is considered to be sufficient to confer protection against disease caused by the measles virus.

The protective data for this widely differing set of diseases is indicative of the ability to protect a vertebrate against any disease caused by an infectious agent, using DNA encoding an antigen from the infectious agent.

Rejection of Claims 1-3, 5-7, 9-26, 28-38 and 40-56 under 35 U.S.C. 112, first paragraph

The Examiner rejected 1-3, 5-7, 9-26, 28-38 and 40-56 for the reasons set forth in the objection to the Specification. In view of the discussion presented above, this rejection is obviated.

Rejection of Claims under 35 U.S.C. 103

Applicants note that the Examiner has not addressed or reiterated certain rejections under 35 U.S.C. 103 from the previous Office Action (Paper Number 11). In particular, the Examiner did not state whether the following rejections were maintained or withdrawn:

the rejection of Claims 1-7, 10-14, 16-22, 24-26, 29-38, 41-49 and 51-56 under section 103, as being unpatentable over Felgner (WO 90/11092) in view of Huylebroeck et al.

(Technological Advances in Vaccine Development, 1988), as set forth in paragraph 10;

the rejection of Claims 15 and 23 under section 103, as being unpatentable over Felgner (WO 90/11092) in view of Tang (Nature 356:152-154 (1992), as set forth in paragraph 11; and

the rejection of Claims 9, 28, 40 and 50 under section 103, as being unpatentable over Felgner (WO 90/11092) in view of Haynes (WO 93/17706), as set forth in paragraph 13.

Applicants respectfully request that the Examiner indicate whether these rejections have been withdrawn, or are maintained.

Rejection of Claims 1-3, 5-7, 10-14, 16-22, 24-26, 29-38, 41-49, and 51-56

The Examiner rejected 1-3, 5-7, 10-14, 16-22, 24-26, 29-38, 41-49, and 51-56 as being unpatentable over Felgner (WO 90/11092) in view of Hunt et al. (J. Virology 62(8):3014-3019 (1988), reference AY). The Examiner stated that:

[I]t would have been obvious to one of ordinary skill in the art to use the gene encoding influenza virus hemagglutinin H7 of Hunt et al. in the plasmid vector of Felgner with a reasonable expectation of eliciting a protective immune response since the vector of Felgner could produce sufficient levels of protein *in vivo* to produce such a response. One would have been motivated to make this modification since it would reduce the chance of causing tumors *in vivo* caused by retroviral vectors.

Applicants respectfully disagree with this assessment.

Obviousness under 35 U.S.C. 103 is a question of law based on the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966):

Under 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy (citation omitted).

The scope and content of the prior art, differences between the prior art and the claims at issue and the level of ordinary skill in the pertinent art, and secondary considerations, as they relate to the subject invention, are each addressed in turn.

First Factor: Scope and Content of Prior Art

Felgner et al. (WO 90/11092, assigned to Vical, Inc.) describes methods of delivering RNA or DNA polynucleotides into a vertebrate cell by delivery into the interstitial space (i.e., into the intercellular, fluid matrix among the fibers of organ tissues or fibers in the walls of vessels or chambers, or within connective tissue or bone, as described at page 23, lines 8-23), for vaccination or gene therapy. Felgner et al. state that various routes of administration and pharmaceutically acceptable vehicles can be used, and focus on use of the methods for transient gene therapy to treat genetically-based diseases such as muscular dystrophy, cystic fibrosis, genetic defects of intermediary metabolism, Alzheimer's disease, liver and lung disease caused by alpha-1-antitrypsin deficiency, and cancers. Felgner et al. also hypothesize that transient gene therapy can be used to increase the resistance of an AIDS patient to HIV infection. In order to increase the resistance of an AIDS patient to HIV infection, Felgner et al. proposed that T cells from the AIDS patient be isolated, transfected with an AIDS resistance gene, and then reintroduced back into the patient. Felgner et al. do not provide any support or data for this hypothetical gene therapy.

In the exemplification, Felgner et al. describe mRNA vaccination of mice to produce gp120 protein of the human immunodeficiency virus (HIV), and eliciting of an antibody response. Felgner et al. do not teach or describe use of any other antigen from any other infectious agent, besides gp-120 from HIV. Felgner et al. do not describe any protective immune response.

Hunt et al. describe immunization of chickens against influenza with a replication-competent retrovirus vector, and subsequent protection against disease when the chickens were challenged with influenza virus. Thus, Hunt et al. describe a vector, whose use results in expression of the influenza

virus hemagglutinin by conventional methods. Hunt et al. do not teach or describe immunization with a DNA transcription unit (i.e., DNA that encodes solely a promoter region and an antigen of the infectious agent). Hunt et al. do not teach or describe any disease other than influenza.

Second and Third Factors: Differences Between the Prior Art and the Claims at Issue and Level of Ordinary Skill in the Art

The claims at issue in the subject application are directed to immunization of a vertebrate by a DNA transcription unit, with the result that the vertebrate is protected against disease.

No teaching or suggestion supporting the combination of the references is found in the prior art of record. Felgner et al. do not teach or suggest that one of ordinary skill should look to a reference concerning influenza: in fact, Felgner et al. do not mention influenza at all, but focus primarily on gene therapy. Hunt et al., who describe the use of a replication-competent vector for vaccination against influenza, do not teach or suggest that one of ordinary skill should look to a reference pertaining to use of non-replication competent polynucleotides for gene therapy or vaccination. Thus, one of ordinary skill in the art would not have been motivated to combine the teachings of Felgner et al. with those of Hunt et al.

The Examiner stated that one of ordinary skill in the art would have been motivated to combine the references, in order to reduce the chance of causing tumors *in vivo* caused by retroviral vectors. However, at the time the invention was made, it was thought that it was necessary to use an infectious agent that was self-replicating in order to produce the level of protein that was thought to be necessary for protection against disease. Therefore, one of

ordinary skill in the art would not have looked to the teachings of Felgner et al., which pertain to non-infectious non-replicating vectors, but would instead have looked for alternative infectious, self-replicating vectors for use in vaccination. Furthermore, there is debate in the art concerning whether the possibility of causing tumors by the use of retroviral vectors is, in fact, any danger. See, for example, "Safety Considerations in Somatic Gene Therapy of Human Disease with Retorvirus Vectors," by H.M. Temin (*Human Gene Therapy* 1:111-123 (1990), a copy of which is attached as Exhibit B), which states that proper design of retrovirus vectors and delivery systems removes most potential foreseen risks of using the vectors in gene therapy. Applicants respectfully request that the Examiner provide support for his position.

Even if the teachings of Felgner et al. are combined with those of Hunt et al., the current invention would not have been obvious, as there is no reasonable likelihood of success in achieving a protective response to immunization with the current methods, viewed in the light of the prior art. Felgner et al. describe introduction into a mouse of a construct that encodes a protein which is pathogenic to humans but not to mice; therefore, the teachings of Felgner et al. cannot show protection. Furthermore, Felgner et al. showed only an antibody response to the gp120 protein. It is known in the art that the presence of antibody to HIV proteins in no way indicates protective immunity (see p. 477 of Kuby, J., *Immunology*, submitted as Exhibit C). Therefore, one of ordinary skill in the art would not have had a reasonable expectation of success in protecting against disease upon challenge.

In addition, the teaching at the time of the invention was that microgram ( $10^{-6}$  gram) quantities of protein would have been necessary to provide protective immunization (see Fields, Virology, Vol. I, Orthomyxoviruses, pp. 1126-1127,

concerning the amounts of protein used in inactivated influenza virus vaccines to obtain protection). However, only picogram ( $10^{-12}$  gram) levels of protein expression resulted from the method used in Felgner et al. (see Figure 3 of Felgner et al.). That is, the quantity of protein produced in the Felgner et al. reference was  $10^6$ -fold less than the quantities the art said would have been necessary to provide protection. Thus, contrary to the Examiner's assertion, one of ordinary skill in the art would not have had a reasonable expectation of eliciting a protective immune response, since the vector of Felgner et al. did not produce what was thought to be a sufficient level of protein *in vivo* to produce such a response. One of ordinary skill in the art would not have had a reasonable expectation that such minute levels of protein expression could have achieved protective immunization. Surprisingly, Applicants have used DNA vaccination and provided a protective effect.

#### Fourth Factor: Secondary Considerations

The secondary considerations described in *Graham v. John Deere* have been accorded significant weight by the Federal Circuit, as described in *Glaros v. H.H. Robertson Co.*: "The Federal Circuit has... repeatedly emphasized the importance of the inquiry into secondary considerations, such as the commercial success of the invention and the prior failure of others, as the strongest precaution against judging an invention from the perspective of 20/20 hindsight." (224 USPQ 1037, 1038 (N.D. Ill. 1984), affirmed 230 USPQ 393 (Fed. Cir. 1986)). Further, in *Stratoflex, Inc. v. Aeoroquip Corp.*, the Federal Circuit stated:

It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included. Thus evidence rising out of the so-called "secondary considerations" must always when present be considered en route to a determination of obviousness.... Indeed, evidence of secondary considerations may often be the most

probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.

(218 USPQ 871, 879 (Fed. Cir. 1983)).

Secondary considerations set forth in *Graham v. John Deere* include, but are not limited to, commercial success, long felt but unsolved needs, and failure of others. As shown by the following, the claimed invention has met a long-standing need for improved vaccines, was not expected by those in the field to work, yielded surprising results, and has met with clear commercial success, as evidence by the fact that it is the subject of one of the 10 largest licensing agreements for an American University. It is noteworthy that it has had such commercial success despite the fact that a patent has not yet issued. The commercial success is due to the nature of the claimed invention, and not to any other economic or commercial factors unrelated to the subject matter of the patent application.

Information clearly showing the commercial success of the invention has recently become available. In May, 1996, a 42 million dollar, licensing agreement was reached between University of Massachusetts Medical Center (UMMC) and Pasteur Merieux-Connaught (Pasteur), for exclusive rights to the methods of vaccination of humans encompassed by the claims of the invention. This licensing agreement (the Pasteur agreement) has been described in a national publication which monitors current events in biotechnology as "among the 10 largest biotechnology deals signed by a U.S. university" (BioWorld Today, May 16, 1996, attached as Exhibit D). Nationwide coverage of the agreement occurred: the agreement was described by the Boston Globe (Exhibit E); the Telegraph (Exhibit F); the Worcester Telegram & Gazette (Exhibit G); the Boston Herald (Exhibit H); Reuters (Exhibit I); the American Political Network (Exhibit J); and the Associated

Press, as well as several television news programs and National Public Radio. Pasteur Merieux-Connaught is one of the world's largest vaccine manufacturers (American Political Network, Exhibit J). Furthermore, as described in the accompanying Declaration of Dr. William S. Rosenberg, Director of Licensing & Ventures for UMMC, other large pharmaceutical companies have also expressed interest in the technology. A company in addition to Pasteur also made an offer of terms for a licensing agreement, and companies other than Pasteur are interested in licensing additional uses of the claimed invention, both in humans and in animals.

The Pasteur agreement pertains to use of DNA vaccination technology for humans, and in particular, relates to development of vaccines to protect humans against thirteen different diseases, including influenza, by injection of purified genetic material from the infectious agent. This licensed subject matter is the same as that disclosed and claimed in the current application. Furthermore, as is also stated in the accompanying Declaration of Dr. William Rosenberg, other companies have expressed interest in licensing further subject matter that is not covered by the Pasteur agreement, including veterinary applications of the technology, as well as use of the technology for treating human diseases not included in the Pasteur agreement. The Pasteur agreement, as well as the continued interest by other companies, clearly demonstrates that the current invention has had, and continues to have, significant commercial success. The commercial success of the current invention is due to the nature of the claimed invention, and not to other technical developments or commercial considerations in the field of vaccine technology.

Other secondary considerations also demonstrate the nonobviousness of the claimed invention. There has been a long felt but unfulfilled need in the area of vaccine technology for improved vaccines that have high

immunogenicity, are inexpensive to produce, are easily transported and stored, and minimize the risk of inadvertent infection. The drawbacks to current vaccines include low immunogenicity, particularly for peptide-based vaccines and also for killed-organism vaccines in which conformational epitopes may be distorted; expensive production, transportation and storage, particularly due to the need for refrigeration; and risk of inadvertent infection from live vaccines, as described in the IAC Newsletter Database, TB Weekly for November 13, 1995 (Exhibit K).

Vaccination using DNA, which is the subject of the claims rejected in the current application, addresses the deficiencies of presently used peptide- or killed-organism-based vaccines, and provides additional advantages. As further described in the IAC Newsletter (Exhibit K), DNA vaccines are inexpensive to produce, are stable without refrigeration, and do not cause inadvertent infection. Furthermore, DNA vaccines may provide improved vaccine efficacy, lower required dosages, reduced side effects, sustained production and delivery of antigen for a prolonged period of time. These advantages are particularly important for developing regions of the world, where refrigeration of presently available vaccines is difficult or prohibitively expensive. Thus, the claimed methods of immunizing against disease have addressed the long-felt needs of vaccine technology.

The significance of DNA vaccination is further emphasized in Exhibit L (Newsday), published October 3, 1995. There, the writer scoffed at the idea of vaccinating with DNA and stated that one of ordinary skill in the art *would not have expected* vaccination using DNA transcription units to be successful. As stated in Exhibit L,

It wasn't long ago that nobody would have bet a buck on the idea of shooting individual genes - what scientists refer to as 'naked DNA' - directly into people to protect against infection. Some

disease specialists, in fact, bluntly called the idea of injecting DNA into a patient without a protein coat or a virus shell outrageous, or, worse, dangerous. In the last six months, however, researchers have begun doing just that, prompted by successful animal studies that now have scientists using words like 'surprising' and 'revolutionary.'

This report was published over *three and a half years* after Applicants had demonstrated protection using DNA vaccination. This evidence of initial disbelief of those in the field of the invention is highly indicative of the nonobviousness of the invention. The Federal Circuit has stated that "expressions of disbelief by experts constitute strong evidence of nonobviousness" (*Environmental Designs, Ltd. v. Union Oil Co. of Calif.*; 218 USPQ 865 (Fed.Cir. 1983)). The disbelief of researchers is a clear indication that the current invention was a surprising discovery.

The unexpected success of vaccination with DNA is further emphasized by the fact that, even several years after Applicants' application was filed, the technology is still considered to be groundbreaking news in vaccine development. For example, Cable News Network (CNN) characterized the DNA vaccination technology as "a potentially powerful type of vaccine, unlike anything now available" (Transcript of HealthWorks show, CNN, June 18, 1994) (Exhibit M). Even today, the DNA vaccine technology is considered by those in the field to be a significant advancement in the art. As described in the Harvard Health Letter, for March, 1996 (Exhibit N), DNA vaccination to protect against disease is one of "ten new discoveries that [faculty advisors] predict will have a significant and far-reaching impact on human health." Thus, despite initial disbelief, the importance of DNA vaccines has become evident, and has been given professional recognition as a critical technology for vaccine development.

Thus, in view of the differences between the cited art and the pending claims, as well as the secondary

considerations described herein, the current invention would not have been obvious to one of ordinary skill in the art.

Rejection of Claims 15 and 23

The Examiner rejected Claims 15 and 23 as being unpatentable over Felgner et al. and Hunt et al., further in view of Tang (Nature 356:152-154 (1992)). The Examiner stated that:

[I]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the methods described by Felgner and Hunt et al. with the delivery mechanism of Tang, due to the simplicity with which the DNA can be delivered to the animal, with the expectation of eliciting a more potent immune response demonstrated by the gene gun mechanism.

Applicants respectfully disagree. The teachings of Felgner et al. and Hunt et al. are described above. Tang et al. describe immunization of mice with microprojectiles coated with plasmids containing human growth hormone (hGH) gene under the transcriptional control of either the human beta-actin promoter or the cytomegalovirus (CMV) promoter. The mice produced antibody directed against hGH. Tang et al. do not describe protection against disease.

As discussed in detail above, Felgner et al. and Hunt et al. do not render obvious the current invention. The teachings of Tang et al. do not make up for the deficiencies of Felgner et al. and Hunt et al. One of ordinary skill in the art would not have been motivated to use the immunization method described by Tang et al. in the methods of Felgner et al. to protect against disease, as one of ordinary skill in the art would not have expected that it would have been possible to protect against disease using a microsphere-encapsulated DNA transcription unit or any DNA transcription unit.

Rejection of Claims 9, 28, 40 and 50

The Examiner rejected Claims 9, 28, 40 and 50 as being unpatentable over Felgner et al. and Hunt et al., further in view of Haynes (WO 93/17706). The Examiner stated that:

[I]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the methods described by Felgner and Hunt et al. with the genes encoding the simian immunodeficiency virus described by Haynes, recognizing the urgent need for a vaccine against immunodeficiency virus.

Applicants respectfully disagree with this assessment. Haynes describes vaccination against a virus, using a foreign genetic "construction" which includes a "promoter operative in cells of the animal and a protein coding region". The construction is coated onto carrier particles that are small in size in relation to the size of the animal cells. The carrier particles are then accelerated into the animal cells. Haynes describes preparation of the HIV constructions, and introduction of the constructions into cells in culture. Haynes describes delivery of the constructs into mice, and generation of antibodies. Haynes does not describe any simian immunodeficiency virus (SIV) constructs. Haynes does not teach or describe protection against disease.

As described in detail above, Felgner et al. and Hunt et al. do not render obvious the current invention. The teachings of Haynes do not make up for the deficiencies of Felgner et al. and Hunt et al. Neither Felgner et al., Hunt et al., nor Haynes, alone or in combination, describe protection against immunodeficiency virus. Indeed, neither Felgner et al. nor Haynes, which discuss immunodeficiency virus, could have described protection, as both use a mouse model of disease. Because mice do not contract immunodeficiency virus, they cannot be protected against immunodeficiency disease. One of ordinary skill in the art would not have had a reasonable expectation of success in immunizing against an immunodeficiency virus.

Rejection of Claims 1-7, 11-26, 30-38, 42-43 and 52-56 under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner provisionally rejected Claims 1-7, 11-26, 30-38, 42-43 and 52-56 as being unpatentable over claims 1, 2, 4, 7-14 and 17-24 of copending application Serial No. 08/009,833. The Examiner stated that, "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed toward immunization against influenza virus with a DNA vaccine."

Applicants will address this rejection when claims are allowed in Serial No. 08/009,833. If appropriate, a Terminal Disclaimer will be filed.

This provisional rejection differs from those set forth in the previous Office Action (paper number 11). In the current Office Action, the Examiner did not address or reiterate several of the provisional rejections from the previous Office Action. In particular, the Examiner did not state whether the following rejections were maintained or withdrawn:

provisional rejection of Claims 17-18, 21, 24-26 and 31-32 under 35 U.S.C. 101, as claiming the same invention as that of Claims 11-14, 22-23 and 17-18 of copending application Serial No. 08/009,833, as set forth in paragraph 15;

provisional rejection of Claims 1-16, 19-20, 22-23, 27-29 and 32-56 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over Claims 1-2, 3, 7-14 and 17-24 of copending application Serial No. 08/009,833 in view of Ulmer et al., as set forth in paragraph 16;

provisional rejection of Claims 17-18, 21, 24-26 and 30-31 under 35 U.S.C. 102(e), as being anticipated by copending

application Serial No. 08/009,833, as set forth in paragraph 17; and

provisional rejection of Claims 1-16, 19-20, 22-23, 27-29 and 32-56 under 35 U.S.C. 103, as being obvious over copending application Serial No. 08/009,833, as set forth in paragraph 18.

Even though Applicants may not address these provisional rejections until the time when Serial No. 08/009,833 is allowed, Applicants respectfully request that the Examiner indicate whether these rejections have been withdrawn, or are maintained.

Conclusion

In view of the amendments and discussion presented above, the claims are in condition for allowance. Applicants respectfully request that the Examiner reconsider and withdrawn all objections and rejections.

If the Examiner believes that a telephone conversation would expedite prosecution, the Examiner is invited to call Applicants' Attorney at (617) 861-6240.

Respectfully submitted,

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Dated: December 6, 1996